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Radiotherapy for prostate cancer; is it "what you do" or "the way that you do it"? A UK perspective on technique and Quality Assurance

Mason MD¹, Moore R², Jones G³, Lewis G³, Donovan JL⁴, Neal DE⁵, Hamdy FC⁶, Lane JA^{4*}, Staffurth JN^{1*} and the ProtecT study group⁷

*Contributed equally

¹Author for correspondence

Professor Malcolm Mason School of Medicine Cardiff University, Cardiff, UK & Department of Clinical Oncology, Velindre Cancer Centre, Cardiff, United Kingdom

Telephone: +44 29 2031 6964, email: masonmd@cardiff.ac.uk

²Institute of Cancer Research and Royal Marsden Hospitals, Sutton and London, UK

³Department of Medical Physics, Velindre Cancer Centre, Cardiff, UK

⁴School of Social and Community Medicine, University of Bristol, Bristol, UK

⁵Departments of Oncology and Surgery, Addenbrooke's Hospital, Cambridge, UK

⁶Nuffield Department of Surgery, University of Oxford, Oxford, UK

⁷ProtecT study group see acknowledgements

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Abstract

Aims: The treatment of prostate cancer has evolved markedly over the last forty years, including radiotherapy, notably with escalated dose and targeting. However, the optimal treatment for localised disease has not been established in comparative randomised trials. We aim to describe the history of prostate radiotherapy trials, including their QA processes, and compare these with the ProtecT trial.

Materials and methods: The UK ProtecT randomised trial compares external beam conformal radiotherapy, surgery and active monitoring for clinically localised prostate cancer and will report on the primary outcome (disease-specific mortality) in 2016 following recruitment between 1999-2009. The embedded QA programme consisted of on-site machine dosimetry at the nine trial centres, a retrospective review of outlining and adherence to dose constraints based on the trial protocol in 54 participants (randomly selected, around 10% of total randomised to radiotherapy, n = 545). These QA processes and results were compared with prostate radiotherapy trials of a comparable era.

Results: There has been an increasingly sophisticated QA programme in UK prostate radiotherapy trials over the last 15 years reflecting dose escalation and treatment complexity. In ProtecT, machine dosimetry results were comparable between trial centres and with the UK RT01 trial. The outlining review showed that the majority of deviations were clinically acceptable although three (1.4%) may have been of clinical significance and were related to outlining of the prostate. Seminal vesicle outlining varied, possibly due to several prostate trials running concurrently with different protocols. Adherence to dose constraints in ProtecT was considered acceptable with 80% of randomised participants having two or less deviations and PTV coverage was excellent.

Conclusion: The ProtecT trial QA results were satisfactory and comparable to trials of its era. Future trials should aim to standardise treatment protocols and QA programmes where possible to reduce complexities for centres involved in multiple trials.

Trial registration: ISCTRN 20141297

Research Highlights

- The optimal treatment for localised prostate cancer has not been established by randomised evidence
- Radiotherapy can be curative for localised disease
- Trial QA is necessary with increasing radiotherapy dose and complexity
- ProtecT compares active monitoring, radiotherapy and surgery and reports in 2016

- The ProtecT QA programme was comparable to other UK trials of its era with satisfactory results

Introduction

In 2016, the first outcome data from the UK ProtecT trial will be reported. In this landmark UK National Institute for Health Research-funded trial, men with clinically localised prostate cancer were randomised to radical prostatectomy, external beam radiotherapy, or active monitoring [1]. Whether or not there are differences in outcomes between these three approaches, there will undoubtedly be an appraisal of the trial's treatment technique in the light of today's technology, the use of dose escalation in 'conventional' 2 Gy fractions and the quality assurance data. This is inevitable, given that the ProtecT trial is unique in comparing three prostate treatment modalities, probably was only achievable when it was done and in the UK – and so will never be repeated. There have been a several other landmark trials in the UK of radiotherapy for prostate cancer, including the Medical Research Council (MRC) RT01 and PR07 trials, the Cancer Research UK/NIHR Cancer Research Network CHHIP trial, and exploratory data from the MRC STAMPEDE trial [2-5]. This article aims to put these radiotherapy trials into their historical context as a backdrop when the first results of the ProtecT trial are unveiled in 2016.

Radiotherapy for prostate cancer; technology shifts the goalposts

The first descriptions of radiotherapy for prostate cancer come from the early 1900s, when reports of radium needle insertions were published in *the Journal of the American Medical Association* [6]. The advent of external beam radiotherapy during the course of the century led to more patients being treated, but a paucity of evidence. Notable from the era in the 1970's and early 1980's were the Stanford case series of Bagshaw, which laid the foundations of clinical practice [7]. At that time, conventional radiotherapy planning involved a planning cystogram, and the manual definition of radiotherapy fields based - ultimately - on the physician's opinion. The advent of CT planning in the late 1980's radically changed practice, the initial hope being that radiotherapy fields could be made smaller, because the tumour definition was more accurate, and so more normal tissue would be spared. In fact,

1 the hope was based on a false premise, though the reasoning was correct. Tumour definition
2 was much more precise, but in turn radiotherapy fields often became larger, as it was
3 evident, in retrospect, that geographical miss had been more common than was previously
4 supposed [8].
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8 Using CT planning, it was also possible to accurately define the extent of rectum included in
9 a high dose volume, even though there was no obvious consensus as to how much rectal
10 irradiation was 'acceptable'. The new level of accuracy, coupled with isocentric planning and
11 delivery on linear accelerators rather than on cobalt, also permitted another development -
12 conformal radiotherapy. In its early days, this was achieved by the manufacture of
13 customised lead blocks, which were mounted on a tray placed on the linear accelerator
14 head. It was presumed that this would, by reducing the volume of normal tissue irradiated,
15 also reduce radiotherapy side effects, and this was proven in a landmark publication of the
16 first randomised trial comparing conformal and conventional radiotherapy for pelvic tumours
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26 Even in the early days of conformal radiotherapy, another goal was envisaged - that of dose
27 escalation, based on the philosophy that, if a rate of 5% of grade 3-4 late toxicity was
28 "acceptable", and if conformal radiotherapy reduced this rate, it would permit dose
29 escalation, hopefully with improved tumour control, titrated against this "acceptable" level of
30 toxicity. Several randomised trials of dose escalation for prostate cancer were opened in the
31 1990's, following pilot studies which suggested that this approach was safe, and these trials
32 have now all reported outcome data [2,10-13]. Though dose-escalation is now routine
33 practice, it was not state of the art in external beam radiotherapy for prostate cancer at the
34 time when the UK ProtecT study was designed in the late 1990's. Importantly, though
35 several clinical centres had the capacity for conformal radiotherapy, it was by no means
36 uniformly available across the UK, and even CT planning was not universal at that time.
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46 In the ProtecT trial, patients with clinically organ-confined prostate cancer were to be
47 randomised to radical prostatectomy, radical external beam radiotherapy, or active
48 monitoring. The problem for the designers of ProtecT in the late 1990s was how to make the
49 radiotherapy technique as 'future-proof' as possible, against a backdrop of limited or non-
50 existent evidence of long term efficacy. Too conservative, and in the event of radiotherapy
51 turning out to be less effective, the trial would be criticised for under-treating patients. Too
52 aggressive, and it would be criticised for over-treating patients. Another factor in the UK was
53 the increasing use of neo-adjuvant hormone therapy in combination with radiotherapy and
54 whether this was also to be included in the ProtecT trial although this was not standard
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practice in the USA. Other contrasts existed between the UK and the USA in terms of dose escalation; in the US, the dose per fraction was limited to 1.8 Gy and the total dose was being escalated to 78 or 80 Gy [14], whilst in the UK, the dose per fraction was 2 Gy and the total dose was limited to 74 Gy. The latter technique was employed in the MRC's RT01 trial [2], which recruited between 1998-2001 and randomised patients to a 'standard' dose of 64 Gy in 32 fractions, versus an escalated dose of 74 Gy in 37 fractions.

In the event, the technique chosen for ProtecT was similar to that used for RT01, in that it employed (a) neo-adjuvant hormone therapy, and (b) dose escalated radiotherapy to a total of 74 Gy in 37 fractions. There were, however, differences between the two trials; although the treatment was given in two phases, in RT01 the phase II dose was 10 Gy, whereas in ProtecT it was 18 Gy. ProtecT also had organ at risk dose constraints pre-specified, unlike in RT01.

The ProtecT trial recruited patients from late 1999 to early 2009, a period when technical developments in radiotherapy have continued apace. Firstly, came the development of portal imaging - another technology that was far from universal in the UK at the ProtecT trial outset. Then, the first reports of Intensity Modulated Radiotherapy (IMRT) for prostate cancer, and subsequently the use of Image Guided Radiotherapy (IGRT) led to a growing pressure to use these techniques routinely [15,16]. Indeed, the current European Guidelines state that the use of IMRT for prostate cancer radiotherapy should now be standard [17]. Conceptually, the argument for IMRT is compelling, but does that weaken the conclusions from trials which came too early to use it? It could be argued that long term radiotherapy toxicity in trials such as RT01 and ProtecT might have been lessened through the use of IMRT, but in a comparative setting with other modalities, similar arguments could also be made about the evolution of open to robotic prostatectomy.

Evidence versus belief; does definitive local therapy cure prostate cancer?

Internationally, the immense uncertainties around treatment of localised prostate cancer were the context for the first randomised trials in which one arm was - essentially - no treatment. These were studies of radical prostatectomy versus 'watchful waiting'. The latter is a strategy in which treatment is explicitly avoided unless given for symptoms - so by

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implication it is palliative only. Two such trials have reported mature results: the Scandinavian SPCG-4 and the US PIVOT trials.

In SPCG-4, men were diagnosed through clinically apparent, as opposed to PSA screen-detected disease, and were, therefore, often symptomatic. In that trial, 695 men were randomised to radical prostatectomy (n = 347) or watchful waiting (n = 348) with a median follow-up of 12 years. Overall, there was a significant disease-specific survival advantage for men treated with surgery, but a more recent analysis has indicated that this benefit was greatest for men either 65 years old or younger or with intermediate disease risk at diagnosis [18]. In the PIVOT trial, radical prostatectomy (n = 367) was compared with watchful waiting (n = 364) with a primary outcome of all-cause mortality and secondary outcomes of prostate specific mortality, metastases and symptoms in a largely screen-detected population. There was no difference in overall or disease-specific survival at a median of 10 years, but in a sub-group analysis men with a PSA of 10 ng/ml and above or intermediate risk disease had a survival advantage with surgery [19].

These two trials do, at least, provide some degree of proof of concept that definitive therapy might indeed cure, or at any rate prolong the survival of, some men with prostate cancer. However, both were surgical trials; there are no large trials comparing radical radiotherapy to watchful waiting or surgery for localised disease. Radiotherapy after surgery also conferred a clinical progression-free survival advantage in the EORTC 22911 trial over no additional treatment in men younger than 70 years and those with positive surgical margins with pathological T3 disease [20].

In locally advanced disease there are more data pertaining to radiotherapy. In the influential EORTC 22861 trial, men with predominantly locally advanced disease were randomised to radiotherapy, or to radiotherapy and hormone therapy [21]. Overall survival was substantially better in men treated additionally with hormone therapy, but what was the contribution of each? The SPCG-7 and intergroup MRC PR3/PR07 studies randomised men with predominantly localised (SPCG) or predominantly locally advanced (MRC) disease to hormone therapy alone, or to hormone therapy plus radiotherapy. In both trials, men who received radiotherapy had significantly better overall survival than men treated with hormone therapy alone [3,22]. Thus, at least in the context of locally advanced disease, radical radiotherapy prolongs survival and conceivably might cure some men. ProtecT is, however, the only prostate cancer trial in the modern era which compares radiotherapy, surgery and active monitoring - the latter permitting deferred radical therapy, and is almost the only trial comparing surgery and radiotherapy. The two previous randomised trials of surgery versus

radiotherapy in localised or locally advanced disease failed to answer the question as they were too small, and the radiotherapy techniques would be considered suboptimal today [23,24], whilst a further Swedish trial of radiotherapy versus watchful waiting only published quality of life outcomes [25].

The impact of dose escalation and the introduction of quality assurance into UK clinical trials

With the advent of dose escalation came an absolute requirement for ensuring that radiotherapy was meticulously planned according to pre-defined criteria and consistently delivered. This might be taken for granted now, but it was far from self-evident at the time when the RT01 and ProtecT trials were in design. Across the UK there was wide variation in institutional dose and fractionation [26,27]; there were no standard criteria defining prostate volumes, treatment margins, or the sparing of critical normal tissues. Formal quality assurance programmes had been introduced into several of the randomised trials of dose escalation worldwide, but in the UK, the RT01 trial was the first of its kind that had an integrated, formal process of quality assurance [28]. In that trial, prostate volumes were pre-defined (Table 1), and planning margins were similarly defined after categorising patients according to their risk of seminal vesicles involvement, using an algorithm developed by the RTOG [29]. In the ProtecT study, a similar approach was adopted (Table 1) but with specified rectal and bladder dose constraints.

A quality assurance programme with interlinked components was established in both ProtecT and RT01 trials. An early process in both trials was that all clinical centres were visited, and machine quality measured using phantom and other dosimetry [30]. No significant adverse findings were reported from these assessments in the RT01 study (mean dose difference -2%) [31] or the ProtecT study where the mean error in prediction from planned ranged from -4.4% to 0.2% across nine centres (Figure 1).

In the RT01 study, an outlining exercise was performed by each centre with three practice cases, and the results of patient outlining were assessed both prospectively and retrospectively [32]. In the ProtecT study, recruitment started in three pilot centres in 1999 and increased to nine centres between 2002 to 2004. Consequently, as outlining exercises

1 had already been completed by all but one study centre for either or both of the RT01 and
2 CHHIP studies (which recruited between 2002-2006), the focus of the on-trial outlining was
3 through discussions of issues at ProtecT radiotherapy meetings with clinical centres.
4 Subsequently, outlining was retrospectively reviewed by two radiotherapists (JNS and
5 MDM). Three patients from the 'low' and three from the 'moderate' risk group were randomly
6 selected for each centre to represent a total of around 10% of patients randomised to
7 radiotherapy (n = 545). Their CT and outlining data were visualised using the CERR
8 (Computational Environment for Radiotherapy Research) software [33].
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15 Outlining was assessed against criteria in the ProtecT protocol. Outlines were classified
16 according to whether they were satisfactory, "acceptable" (a deviation from the protocol, but
17 acceptable clinical practice), or "unacceptable" (a protocol deviation with potential clinical
18 consequences) and the results are summarised in Table 2. The PTV margins have no errors
19 in outlining in the 108 cases reviewed (two volumes/case). There were some variations from
20 the protocol; however, only three (1.4%) were assessed as potentially being of clinical
21 significance. Two examples of protocol violations in outlining are shown in Figure 2. These
22 were all related to poor outlining of the prostate (Figure 2a), possibly due to insufficient
23 radiological anatomy knowledge or drawing target volumes as this was published in the mid-
24 1990s and may have affected the pilot cases. The majority (15/23, 65%) of acceptable
25 protocol variations were related to incorrect definition of the seminal vesicles and the
26 majority of these (10/16, 63%) were in the definition of the base of the seminal vesicles
27 (Figure 2b). We hypothesise that this relates to the concurrent recruitment to the RT01,
28 CHHIP and ProtecT trials in centres as each trial had different definitions of the volume of
29 seminal vesicles to be included in the base. This issue was not highlighted to clinical
30 investigators at that time.
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43 In the RT01 study, although a prospective outlining exercise was performed, the first of its
44 kind in a UK clinical trial [32], there was no possibility for assessment of adherence to pre-
45 specified dose constraints in organs at risk. In the ProtecT study, adherence to 13 dose
46 constraints, including the bladder (2) and rectum (5), the main organ at risk for treatment
47 toxicity, were assessed by an independent radiotherapy physicist in the same cases
48 selected for outline review, and the results are summarised in Figure 3. Many deviations
49 were driven by clinical necessity, e.g. an unfavourable anatomy. Around 80% of the plans
50 had two or fewer deviations so this was judged to show good overall adherence to the trial
51 protocol. PTV1 coverage was fully met for 89% (46) of plans, with a further three between
52 95.8% and 98.0% and in the remaining three the dose was reduced probably for clinical
53 reasons. Similar results were obtained for PTV2.
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The quality of radiotherapy planning and delivery was judged to be satisfactory in both RT01 and ProtecT trials. Deviation from the protocol has the potential to confound the study question and so quality assurance is, therefore, essential when comparing different treatments and trials. Our analysis of a subset of the radiotherapy plans demonstrates good understanding and adherence to the ProtecT protocol. Since then, pre-specified QA has become a requisite component, and of recent UK prostate trials, the most detailed programme is in the CHHIP study with single phase forward planned three-field IMRT [4].

An outside observer might reasonably (though provocatively) ask; what has QA achieved in this setting? After all, some notable trials identified benefits for radiotherapy (RT) with QA features of their era (e.g. EORTC 2291 or EORTC 22863) sometimes without pre-specified constraints to organs at risk or with outlining reviews conducted retrospectively [2, 20,34]. The answer is twofold. Firstly, a common feature of these studies is that they were variations on a theme of "RT versus no RT"; modern radiotherapy trials either compare radiotherapy with another equivalent modality (ProtecT), or different techniques, doses, or schedules (e.g. RT01 and CHHIP) or the non-randomised comparisons recently published from the STAMPEDE trial [35]. As the trend moves inexorably towards higher total dose equivalents, and fewer fractions [4], the desirability of highest quality treatment delivery becomes an absolute imperative - with much to lose in terms of adverse effects for patients otherwise.

The worldwide perspective and QA implementation in future trials

Worldwide support for QA within radiotherapy trials has differed considerably. The US, via the Radiation Therapy Oncology Group (RTOG), has, with central funding, had formal QA programmes since the 1970's for clinical trials employing radiotherapy with detailed credentialing for trial centres for IMRT trials [36]. Funding from RTOG has allowed on-trial review and analysis of trial outcomes against levels of protocol adherence which has historically been beyond our scope in the UK. The EORTC Radiotherapy Group has also had a comprehensive QA programme since the 1980's with centralised support and infrastructure for radiotherapy trials [37]. In due course it might be possible to analyse treatment failures in relation to the quality of treatment delivery, and ProtecT could be an exemplar when outcome data are available in 2016.

A second key benefit of retrospective analysis of trial QA is learning for the future. It is now clear that groups setting up multiple trials in the same tumour site should aim to minimise differences in radiotherapy techniques between the trials. This has been an ongoing effort within the UK's NCRI RadioTherapy Trials Quality Assurance group with notable successes across trials from different trial groups in rectal, oesophageal and pancreatic cancer trials [38]. However, there are still exceptions especially with large international collaborative trials which have detailed QA programmes but they are not standardised with other trials within a country (e.g. PACE [39]:).

Future Prospects - ProtecT and its impact

An inherent feature of any technology-dependent study is that its technique will become obsolete. That will happen for today's sophisticated studies of IMRT and IGRT as surely as it did for conventional isocentrically planned radiotherapy. There is no doubt that, were trials such as ProtecT to be launched today, the QA programme would look very different to the way in which it was actually done. Will this impact on the interpretation of the ProtecT results, when they are finally released? It is essential that the standards of treatment delivery, whether surgery, radiotherapy (or indeed, active monitoring) are presented clearly and judged by the standards of their time. Against those standards it would seem that the radiotherapy delivery in trials such as ProtecT and RT01 was, at the very least, satisfactory, and will not be a confounding factor when comparisons are made between the three ProtecT treatments for clinical and patient-reported outcomes. How those findings are then related to modern techniques, or to other modalities such as focal therapy, SBRT, or brachytherapy, is a matter for future discussion, but those discussions will undoubtedly be better informed by quality assurance having been embedded in the ProtecT trial.

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Ethics

National Research Ethics approval for the ProtecT trial (MREC01/4/025) and sponsor the University of Oxford.

ProtecT Study Group

Nurses: leads: Sue Bonnington, Lynne Bradshaw, Debbie Cooper, Emma Elliott, Pippa Herbert, Peter Holding, Joanne Howson, Mandy Jones, Teresa Lennon, Norma Lyons, Hilary Moody, Claire Plumb, Tricia O'Sullivan, Liz Salter, Sarah Tidball, Pauline Thompson; *others:* Tonia Adam, Sarah Askew, Sharon Atkinson, Tim Baynes, Jan Blaikie, Carole Brain, Viv Breen, Sarah Brunt, Sean Bryne, Jo Bythem, Jenny Clarke, Jenny Cloete, Susan Dark, Gill Davis, Rachael De La Rue, Jane Denizot, Elspeth Dewhurst, Anna Dimes, Nicola Dixon, Penny Ebbs, Ingrid Emmerson, Jill Ferguson, Ali Gadd, Lisa Geoghegan, Alison Grant, Collette Grant, Catherine Gray, Rosemary Godfrey, Louise Goodwin, Susie Hall, Liz Hart, Andrew Harvey, Chloe Hault, Sarah Hawkins, Sharon Holling, Alastair Innes, Sue Kilner, Fiona Marshall, Louise Mellen, Andrea Moore, Sally Napier, Julie Needham, Kevin Pearse, Anna Pisa, Mark Rees, Elliw Richards, Lindsay Robson, Janet Roxburgh, Nikki Samuel, Irene Sharkey, Michael Slater, Donna Smith, Pippa Taggart, Helen Taylor, Vicky Taylor, Ayesha Thomas, Briony Tomkies, Nicola Trewick, Claire Ward, Christy Walker, Ayesha Williams, Colin Woodhouse, Elizabeth Wyber and others.

Urological surgeons: Jonathan Aning, Prasad Bollina, Jim Catto, Andrew Doble, Alan Doherty, Garrett Durkan, David Gillatt, Owen Hughes, Roger Kocklebergh, Anthony Kouparis, Howard Kynaston, Hing Leung, Param Mariappan, Alan McNeill, Edgar Paez, Alan Paul, Raj Persad, Philip Powell, Stephen Prescott, Derek Rosario, Edward Rowe, Hartwig Schwaibold, David Tulloch, Mike Wallace.

Oncologists: Amit Bahl, Richard Benson, Mark Beresford, Catherine Ferguson, John Graham, Chris Herbert, Graham Howard, Nick James, Alastair Law, Carmel Loughrey, Malcolm Mason, Duncan McClaren, Helen Patterson[†], Ian Pedley, Angus Robinson, Simon Russell, John Staffurth, Paul Symonds, Narottam Thanvi, Subramaniam Vasanthan, Paula Wilson. [†] Dr Patterson died in April 2012.

Radiotherapy and medical physics: Helen Appleby, Dominic Ash, Dean Aston, Steven Bolton, Graham Chalmers, John Conway, Nick Early, Tony Geater, Lynda Goddall, Claire Heymann, Deborah Hicks, Liza Jones, Susan Lamb, Geoff Lambert, Gill Lawrence, Geraint Lewis, John Lilley, Aileen

MacLeod, Pauline Massey, Alison McQueen, Rollo Moore, Lynda Penketh, Janet Potterton, Neil Roberts, Helen Showler, Stephen Slade, Alasdair Steele, James Swinscoe, Marie Tiffany, John Townley, Jo Treeby, Joyce Wilkinson, Lorraine Williams, Lucy Wills, Owain Woodley, Sue Yarrow.

Histopathologists: Selina Bhattarai, Neeta Deshmukh, John Dormer, Malee Fernando, John Goepel, David Griffiths, Ken Grigor, Nick Mayer, Jon Oxley, Mary Robinson, Murali Varma, Anne Warren.

Research and data management: Lucy Brindle, Michael Davis, Dan Dedman, Elizabeth Down, Hanan Khazragui, Chris Metcalfe, Sian Noble, Tim Peters, Hilary Taylor, Emma Turner, Julia Wade, Eleanor Walsh

Administrative support: Susan Baker, Elizabeth Bellis-Sheldon, Chantal Bougard, Joanne Bowtell, Catherine Brewer, Chris Burton, Jennie Charlton , Nicholas Christoforou, Rebecca Clark, Susan Coull, Christine Croker, Rosemary Currer, Claire Daisey, Gill Delaney, Rose Donohue, Jane Drew, Rebecca Farmer, Susan Fry, Jean Haddow, Alex Hale, Susan Halpin, Belle Harris, Barbara Hattrick, Sharon Holmes, Helen Hunt, Vicky Jackson, Donna Johnson, Mandy Le Butt, Jo Leworthy, Tanya Liddiatt, Alex Martin, Jainee Mauree, Susan Moore, Gill Moulam, Jackie Mutch, Kathleen Parker, Christopher Pawsey, Michelle Purdie, Teresa Robson, Lynne Smith, Carole Stenton , Tom Steuart-Feilding, Chris Sully, Caroline Sutton, Carol Torrington, Zoe Wilkins, Sharon Williams, Andrea Wilson and others.

Data Monitoring Committee: Chairs: Adrian Grant and Ian Roberts, Deborah Ashby, Richard Cowan, Peter Fayers, Killian Mellon, James N'Dow, Tim O'Brien, Michael Sokhal

Trial Steering Committee Chair: Michael Baum, Jan Adolfson, Peter Albertsen, David Dearnaley, Fritz Schroeder, Tracy Roberts, Anthony Zietman

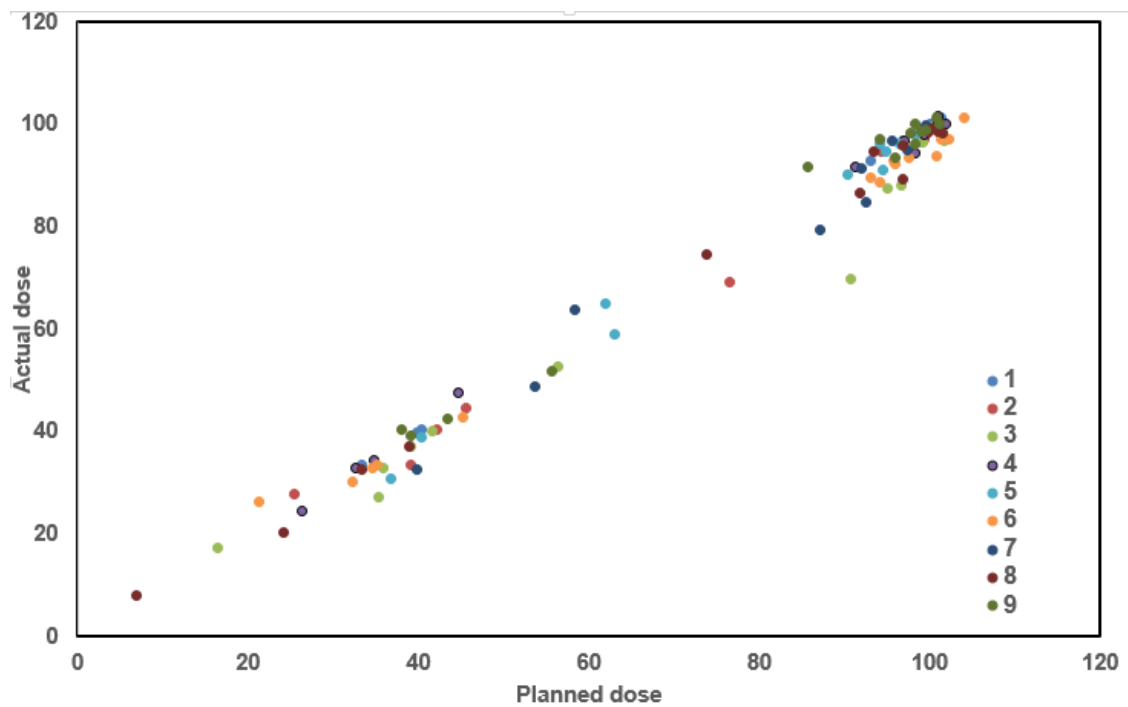
Table 1: Target volumes, treatment margins and dose constraints in the RT01 and ProtecT protocols

Parameter	RT01 (74 Gy arm)	ProtecT
Risk category	Roach formula (Low & Moderate risk groups)	Roach formula (Low & Moderate risk groups)
Phase I CTV	Prostate and base SV + 0.5 mm (L) or SV (M)	Prostate & base SV (L) or SV (M), Constraint: no margin beyond organ
Phase I PTV	CTV1 + 5-10 mm	CTV1 + 10 mm
Phase II CTV	Prostate	Prostate, Constraint: no margin beyond organ
Phase II PTV	As per CTV	CTV2 + 5 mm
Phase I dose and fractionation	64 Gy in 32#	56 Gy in 28# (PTV1 V95%, 53.2Gy)
Phase II dose and fractionation	10 Gy in 5#	18 Gy in 9# (PTV2 V95%, 17.1Gy)
Summed dose constraints		
Unique gantry angles		3 or 4
		ICRU max D1.8cc ≤105% (77.7 Gy)
Bladder	Not to exceed prescribed dose to isocentre	V74Gy <25%
		V67Gy <50%
Rectum	None specified	V74Gy ≤3%
		V70Gy <25%
		V67Gy <30%
		V55.5Gy <50%
		Minimum AP separation of 44Gy isodose and posterior rectal contour along midline >0 mm
Femoral heads	None specified	D2cc <55Gy left and right

Table 2: Retrospective outlining assessment in the ProtecT trial

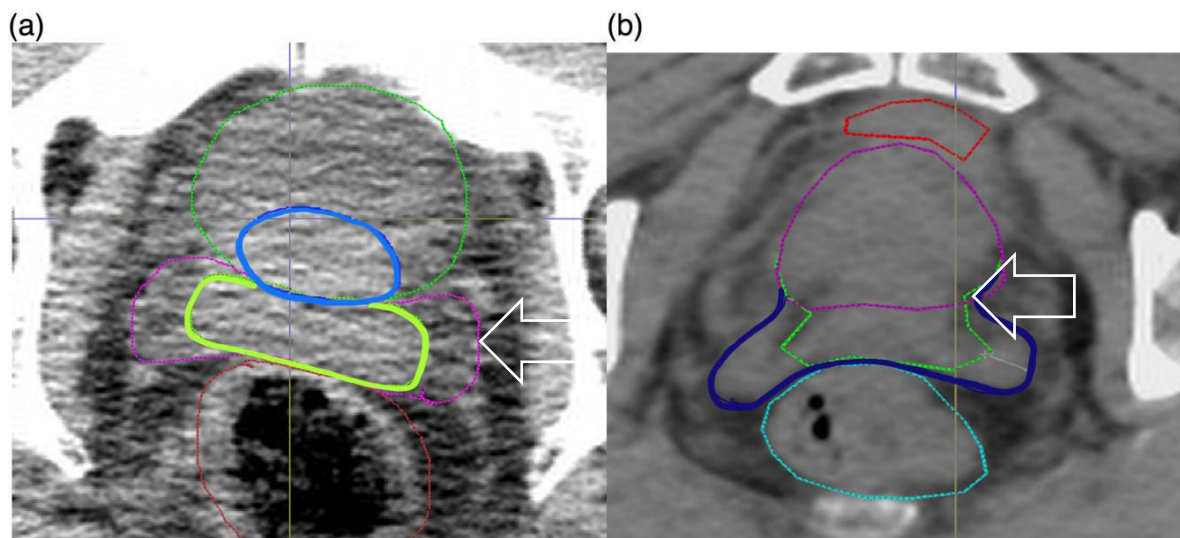
Target volume (number assessed)	Prostate (54)	Seminal vesicles (54)	Bladder (54)	Rectum (54)	Total (216)	Percentage (%)
Satisfactory	40	35	53	40	168	77.8%
Acceptable variation	2	15	1	4	22	10.2%
Unacceptable variation						
Clinical significance:						
Unlikely	9	4	0	10	23	10.6%
Possible	3	0	0	0	3	1.4%
Total	54	54	54	54	216	100%

Figure 1: Phantom dosimetry results from the nine ProtecT centres



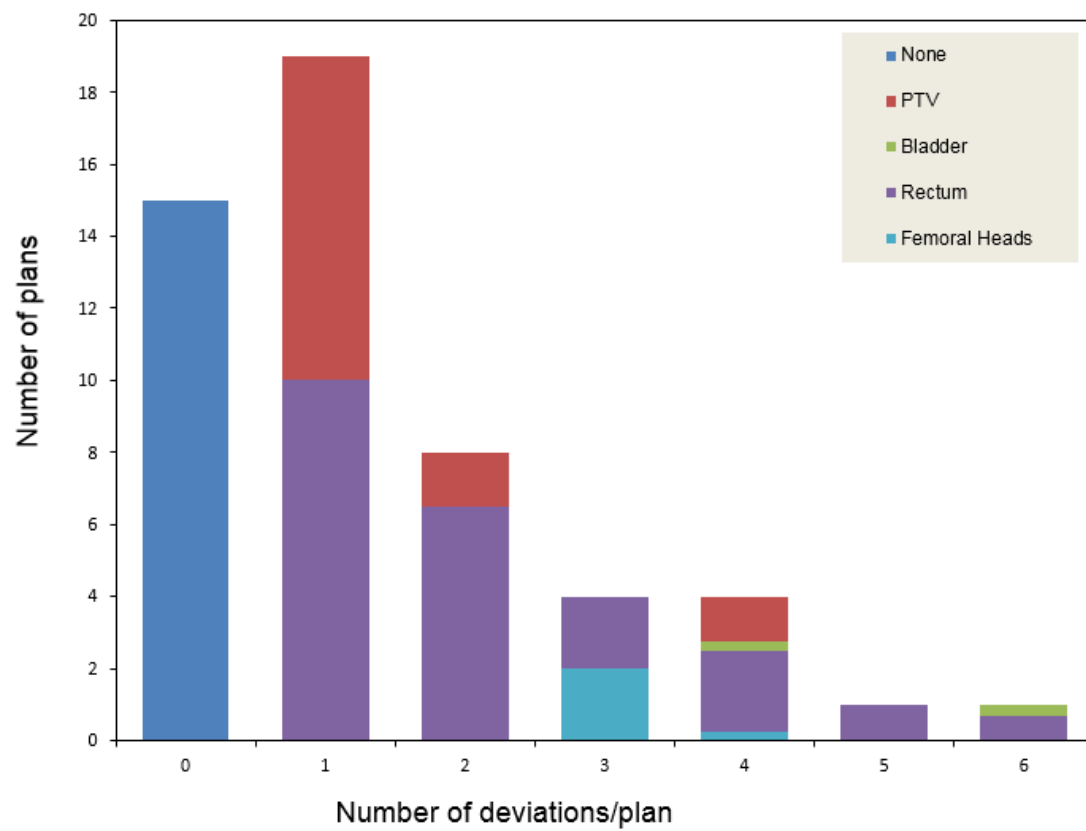
The planned dose normalised for an error-free planning system and setup with negligible measurement error is plotted against actual dose by centre (1-9) measured using an anthropometric phantom. Doses at seven points around the prostate and irradiated volumes were predicted (using the centre system) and measured for both phases.

Figure 2 Examples of protocol variations in outlining in the ProtecT trial



CT slices from two volumes drawn by clinicians from two centres to illustrate protocol variations of potentially clinical significance. (a) The investigator has not outlined any CTV on this slice. The reviewers opinion of the correct CTVprostate is shown in blue, this protocol variation was viewed to be a potentially clinically significant error. The investigator CTVseminal vesicles outline is shown in purple (marked with arrow). The reviewers CTVseminal vesicle outline is shown in light green; this was classified as a clinical error, but was felt unlikely to have clinical consequences. (b) Investigator outline of CTVseminal vesicles (light green, marked with arrow) does not encompass all the seminal vesicles whereas the reviewers outline of the seminal vesicles is shown in the dark blue line, this protocol variation was viewed as a clinical error, but unlikely to have clinical significance.

Figure 3. Compliance with rectal, bladder, femoral heads and PTV dose constraints in the ProtecT trial



Two plans from one centre did not have dose data so were excluded from the total 54 plans.

Conflict of interest

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